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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/747,029	UNION ET AL..2	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8,9,12-14,18,20,23,28 and 29* is/are pending in the application.

4a) Of the above claim(s) *23,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,9,12-14,18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 11/20/03 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election of Group X drawn to a cyclic peptide comprising the primary amino acid structure consisting of SEQ ID NO: 4, a composition thereof, and immunotoxin comprising said peptide, and composition thereof, and kit comprising said peptide, and species of SEQ ID NO: 12 in Paper No.17.

3. Applicant is reminded that claim 23 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons, and newly submitted claims 28 and 29 which depend on claim 23 is distinct for the same reasons:

Claim 23 is drawn to a method for detecting antibodies present in sera from patients with RA using a peptide, classified in Class 435, subclass 7.1, whereas the instant claims of elected Group X are drawn to a cyclic peptide/composition thereof, and immunotoxin comprising said peptide, and composition thereof, and kit comprising said peptide, classified in Class 530, subclasses 317, 345 and 402 and Class 435, subclass 975.

The invention of Group X and that of claim 23 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)).

In the instant case, the product as claimed can be used in a materially different process such as immunopurification procedures or as an immunogen.

Therefore, they are patentably distinct.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 23 remains withdrawn and claims 28 and 29 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP §

Claims 5-7, 10, 11, 15-17, 19, 21 and 22 have been canceled.

Claims 1-4, 8, 9, 12-14, 18 and 20 are currently being examined.

4. Upon consideration of a search of the prior art, since SEQ ID NO: 4 and 12 appear to be free of the prior art, the search has been extended to include SEQ ID NO: 17 recited in instant claim 9.

The following are new grounds of rejection necessitated by Applicant's amendment filed 11/20/03.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, 8, 9, 12-14, 18 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The specification does not disclose how to make/and or use the claimed peptide/immunotoxin/composition thereof comprising the amino acid sequence of SEQ ID NO: 12 or SEQ ID NO: 17, nor consisting of 18 amino acids and having the primary structure recited in instant claim 1, including for use in a kit for detecting rheumatoid arthritis. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass peptides that are not specifically recognized by autoimmune antibodies from patients suffering from rheumatoid arthritis (RA).

The instant claims encompass minimally a peptide that is 18 amino acid residues in length or longer, and the open transitional phrase comprising recited in claim 9 encompasses peptides longer than 18 that are used for detection of rheumatoid arthritis. There is insufficient disclosure in the specification on said peptides.

The specification discloses peptides of less than 50 amino acids that contain a peptide turn comprising at least one citrulline residue, less than 12 amino acid residues between two cysteine residues with said citrulline residue being one of the amino acids between the said cysteine residues and the said peptide being specifically recognized by autoimmune antibodies from patients suffering from RA (page 5 at lines 13-19). The specification discloses that the peptides have a length of preferably 40, 30, 25, 20 or less amino acids (page 7 at lines 23-26). The specification further discloses that the said peptides have a length between 13 and 19 amino acids (page 10 at lines 9-11). The specification discloses peptides with motifs 18 amino acids or less in length recited and peptides with complete sequences of 18 amino acids in length recited in instant claim 9.

The specification further discloses the criteria essential for accomplishing a three-dimensional structure and immunoreactivity with autoantibodies present in sera from RA patients (paragraph spanning pages 15 and 16 and continuing on pages 16 and 17) in type I peptides which have 6 amino acid residues between Cys residues, and those criteria essential in type II peptides which have 4 amino acid residues between Cys residues (lines 11-25 on page 17 and page 18 and page 19 at lines 1-5). However, the specification discloses these criteria only for

peptides that are up to and including 18 amino acid residues in length, and includes possible amino acid substitutions at various positions in the peptides.

The specification discloses (on page 2 at line 24-31 and continuing on to page 3 at lines 1-3) that serological support for diagnosing RA is not very well established and is based mainly on the presence of rheumatoid factors (RF), that a number of RA patients are RF negative while RF is also found in a variety of other rheumatic diseases. The specification further discloses (on page 13 at lines 12-30 and page 14 at line 31) that a set of citrullinated peptides generated using molecular modeling and computational chemistry which are reactive with the autoimmune antibodies have a similar three-dimensional structure comprising a peptide turn. The specification discloses testing a number of previously diagnosed (on the basis of ACR criteria) RA patients' sera for reactivity with multiple citrullinated peptides of the invention (on page 35-41). The specification discloses a high specificity for reactivity of the peptides with the RA sera and complementarity with the RF test. The specification does not disclose treating rheumatoid arthritis or any other autoimmune disease in a subject animal, nor diagnosing patients with rheumatoid arthritis or any other autoimmune disease.

Evidentiary reference Jaarsveld et al (Clin Exp Rheum 1999, 17: 689-697, IDS reference) teaches that the CCP-ELISA (CCP, a cyclic citrullinated peptide) detects antibodies which recognize a subset of antiperinuclear factor and AKA (APF, profilaggrin, a potential prognostic marker for RA) determinants and that the reactivity of RA sera to different citrullinated peptide variants is highly diverse (especially page 695 at columns 1 and 2). Jaarsveld et al further teach that testing for APF by indirect immunofluorescence and the CCP-peptide ELISA assay together may have prognostic value to predict mild rheumatoid arthritis disease, but that reliable identification at baseline of individual patients with progressive disease is still not possible (especially Abstract). Jaarsveld et al also teaches that rheumatoid arthritis patients are a heterogeneous population (especially page 695 and 696); for example with respect to radiological damage scores the combination of RF and APF is a better prognostic marker than the single tests alone (especially page 696 at column 1, first paragraph). Evidentiary reference Schellekens et al (Arthritis & Rheum, 2000, 43(1): 155-163, IDS reference) teaches that although the anti-CCP ELISA assay is highly specific for rheumatoid arthritis, that further studies are clearly needed to substantiate the prognostic values of the anti-CCP assay, and that combining the anti-CCP assay with the IgM-RF ELISA increased the positive predictive value (especially page 162 at the last column).

Evidentiary reference Schellekens et al teaches that the anti-CCP ELISA was specific for established RA sera and moderately sensitive, and combined with the IgM-RF ELISA resulted in a higher positive predictive value, than using the IgM-RF ELISA alone (especially abstract). Schellekens et al further teaches peptide cfc1-cyc which is identical to peptide 1546 (SEQ ID NO: 22) of the instant specification, with one additional amino acid residue at the amino terminus, and which does not have less than 12 amino acid residues between cys residues. The instant specification discloses that peptide 1546 was comparable in sensitivity to the peptides 1611, 1646, 1650 and 1651 (table 7) which were cited by Applicant as superior in the

amendment filed 12/2/02. Accordingly, there is a high level of unpredictability in diagnosing subjects with autoimmune diseases including rheumatoid arthritis using the claimed citrullinated peptides and Applicant does not provide direction or guidance to do so.

There is no guidance in the specification in peptides longer than 18 amino acid residues as to what amino acid residues outside of the core motif-containing amino acid residues result in a functional peptide, i.e., which amino acid residues preserve the desired three dimensional structure. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain functional activity, and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e., its activity) are not well understood and are therefore not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, Merz & LeGrand, Birkhauser Boston, pages 491-495, 1994, entire article, especially Section 6, paragraph 1), it would require undue experimentation for one of skill in the art to arrive at amino acid sequences that would have functional activity. In other words, since it would require undue experimentation to identify amino acid sequences that have functional activity, it would require undue experimentation to make the corresponding sequences.

Accordingly, there is a high level of unpredictability in making and/or using the claimed citrullinated peptides and Applicant does not provide direction or guidance to do so. There is insufficient guidance in the specification as to how use the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 9 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is indefinite in the recitation of "comprising " because it is not clear what is meant. Base claim 1 recites "A peptide consisting of 18 amino acids" and the peptide "comprising the amino acid sequence" recited in claim 9 is 18 amino acid residues in length.

9. SEQ ID NO: 4, 12 and 17 appear to be free of the prior art.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end

of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday and Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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